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Research Letter | Pharmacy and Clinical Pharmacology

Safety of JN.1-Updated mRNA COVID-19 Vaccines

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Introduction

Updated mRNA COVID-19 vaccines targeting the SARS-CoV-2 Omicron JN.1 lineage were recently authorized in the US and Europe[1,2] and made available as the 2024-2025 season booster dose in many countries. Data to support their safety are scarce. This nationwide cohort study investigated the association between vaccination with JN.1-containing vaccines and the risk of 29 serious adverse events.

Methods

The study cohort was established through linkage of individual-level data from nationwide health care registers. Danish law exempts register-based research in Denmark from informed consent and ethics committee approval. This study is reported following the STROBE reporting guideline.

All adults in Denmark recommended to receive the 2024-2025 JN.1-containing booster vaccine (ie, those aged ≥65 years or individuals in high-risk groups) who had previously received 3 or more

Table. Study Cohort Characteristics

Characteristic[a]	Individuals, No. (%)		
	Entire study cohort (N = 1 585 883)	Vaccinated with JN.1-containing vaccine (n = 1 012 400)	Not vaccinated with JN.1-containing vaccine at study end (n = 573 483)
Age, mean (SD), y	66.8 (14.5)	73.5 (10.3)	60.6 (17.1)
Sex			
Female	862 585 (54.4)	547 550 (54.1)	315 035 (54.9)
Male	723 298 (45.6)	464 850 (45.9)	258 447 (45.1)
Region of residency			
Capital Region of Denmark	437 167 (27.6)	274 017 (27.1)	163 150 (28.4)
Central Denmark Region	358 459 (22.6)	233 305 (23.0)	125 154 (21.8)
Northern Denmark Region	173 947 (11.0)	110 645 (10.9)	63 302 (11.0)
Region Zealand	255 036 (16.1)	166 728 (16.5)	88 308 (15.4)
Region of Southern Denmark	361 232 (22.8)	227 693 (22.5)	133 539 (23.3)
Region not specified	42 (<0.1)	12 (<0.1)	30 (<0.1)
Vaccination priority groups			
Age priority	1 145 608 (72.2)	877 529 (86.7)	268 079 (46.7)
High-risk priority	440 275 (27.8)	134 871 (13.3)	305 404 (53.3)
Comorbidities			
Asthma	54 596 (3.4)	31 099 (3.1)	23 497 (4.1)
Chronic respiratory disorder	64 802 (4.1)	46 563 (4.6)	18 239 (3.2)
Chronic cardiac disorder	298 513 (18.8)	205 581 (20.3)	92 932 (16.2)
Kidney disorder	26 021 (1.6)	16 877 (1.7)	9144 (1.6)
Diabetes	111 169 (7.0)	64 944 (6.4)	46 225 (8.1)
Autoimmune disorder	158 145 (10.0)	85 931 (8.5)	72 214 (12.6)
Epilepsy	15 493 (1.0)	9957 (1.0)	5536 (1.0)
Malignant neoplasm	157 967 (10.0)	100 085 (9.9)	57 882 (10.1)
Psychiatric disorder	113 395 (7.2)	61 245 (6.0)	52 150 (9.1)

[a] The start of the study period was May 1, 2024, while the rollout of the JN.1-containing booster vaccine was initiated at approximately the start of October 2024, and the study period ended on March 31, 2025.

+ Supplemental content

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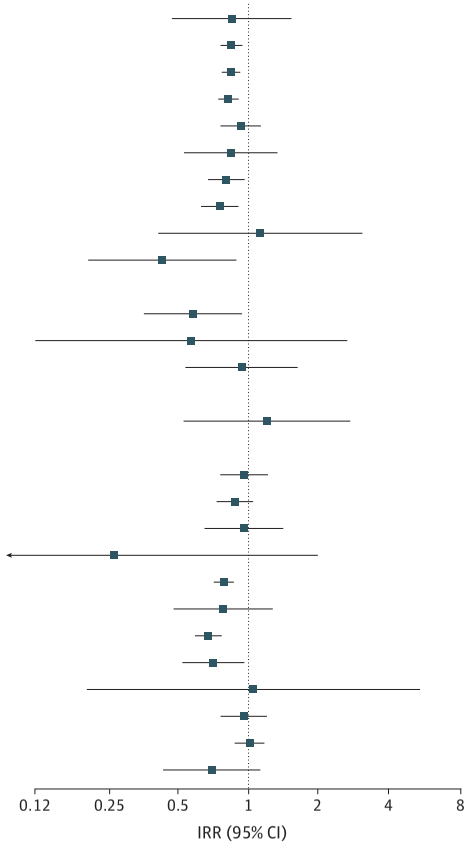
Figure. Risk of Adverse Events After Booster Vaccination With JN.1-Containing Vaccines

Outcome	No. events/person-year		28-d IR per 100 000 person-years		IRR (95% CI)
	With JN.1 (risk period)	Reference period	With JN.1 (risk period)	Reference period	
Anaphylaxis	14/77 392	284/1 310 682	1.4	1.7	0.85 (0.47-1.53)
Ischemic cardiac event	432/73 823	8052/1 253 888	44.9	49.2	0.84 (0.76-0.94)
Cerebrovascular event	625/74 262	10 379/1 263 857	64.5	63.0	0.84 (0.77-0.92)
Cerebrovascular infarction only, including TIA	509/74 651	8 775/1 269 768	52.3	53.0	0.82 (0.74-0.91)
Intracranial bleeding	136/77 106	1877/1 306 552	13.5	11.0	0.92 (0.76-1.13)
Arterial thromboembolism	24/77 413	379/1 311 127	2.4	2.2	0.84 (0.53-1.33)
Deep venous thrombosis	152/76 405	2847/1 294 941	15.3	16.9	0.80 (0.67-0.96)
Pulmonary embolism	144/76 566	2909/1 297 535	14.4	17.2	0.75 (0.62-0.90)
Myocarditis	5/77 489	76/1 312 177	0.5	0.4	1.12 (0.41-3.10)
Pericarditis	8/77 417	338/1 310 773	0.8	2.0	0.42 (0.20-0.89)
Cerebral venous thrombosis	0/77 497	37/1 312 506	0.0	0.2	NE
TC and coagulative disorders	19/77 306	664/1 307 867	1.9	3.9	0.58 (0.35-0.94)
Guillain-Barré syndrome	2/77 493	47/1 312 432	0.2	0.3	0.57 (0.12-2.66)
Bell palsy	16/77 403	329/1 310 742	1.6	1.9	0.93 (0.53-1.63)
Transverse myelitis	0/77 502	15/1 312 535	0.0	0.1	NE
Encephalomyelitis or encephalitis	8/77 481	111/1 312 200	0.8	0.6	1.20 (0.52-2.74)
Narcolepsy	0/77 499	16/1 312 504	0.0	0.1	NE
Appendicitis	90/77 007	1614/1 303 759	9.0	9.5	0.96 (0.75-1.21)
Aseptic arthritis	157/76 230	3056/1 292 170	15.8	18.1	0.87 (0.73-1.05)
Type 1 diabetes	32/76 486	742/1 289 309	3.2	4.4	0.95 (0.65-1.41)
Subacute thyroiditis	1/77 479	107/1 312 108	0.1	0.6	0.26 (0.03-1.99)
Heart failure	516/74 606	9 315/1 268 525	53.0	56.3	0.78 (0.71-0.86)
Acute liver failure	20/77 425	456/1 311 187	2.0	2.7	0.78 (0.47-1.27)
Acute kidney failure	281/76 250	6108/1 292 463	28.3	36.2	0.67 (0.59-0.77)
Acute pancreatitis	51/77 186	1112/1 307 209	5.1	6.5	0.70 (0.52-0.96)
Erythema multiforme	2/77 501	25/1 312 561	0.2	0.1	1.05 (0.20-5.49)
Seizure	100/76 705	1554/1 299 552	10.0	9.2	0.95 (0.76-1.20)
Arterial aneurysm	251/75 990	3365/1 290 912	25.3	20.0	1.01 (0.87-1.17)
Uveitis	20/77 314	546/1 309 068	2.0	3.2	0.69 (0.43-1.12)



The figure shows adjusted incidence rate ratios (IRRs) for 29 adverse events of special interest to COVID-19 vaccines; rates observed during the 28-day risk period after booster vaccination with updated mRNA COVID-19 vaccines containing the SARS-CoV-2 Omicron JN.1 lineage (KP.2 strain) are compared with rates during the reference period. Each outcome was studied separately, resulting in potential differences in denominators due to varying exclusions. IR indicates crude incidence rate; NE, not estimable; TC, thrombocytopenia; TIA, transient ischemic attack.

COVID-19 vaccine doses were included. The study period ran from May 1, 2024, to March 31, 2025. Vaccination status during follow-up was classified as a time-varying variable (eTable in Supplement 1).

We analyzed 29 adverse outcomes adapted from prioritized lists of adverse events of special interest to COVID-19 vaccines. Each adverse event was analyzed separately. Adverse events were identified as the first hospital contact with a recorded outcome diagnosis, with the date of diagnosis considered the event date (eTable in Supplement 1).[3-6] During the study period, individuals were followed up until first outcome event while censoring upon emigration, death, or the end of the study period. Outcome rates during the first 28 days after JN.1-containing vaccine administration (ie, the risk period) were compared with outcome rates during the remaining period (ie, the reference period, with follow-up from the study start or ≥43 days after any prior dose or the JN.1-containing vaccine dose) as previously described (eFigure in Supplement 1).[5,6] If uncensored, individuals could contribute person-time to 28-day risk and reference periods. We compared risk and reference period outcome rates using Poisson regression to estimate incidence rate ratios adjusted for sex, age, region, vaccination priority group, calendar time, and number of comorbidities. Statistical tests were 2-sided and conducted in R statistical software version 4.1.1 (R Project for Statistical Computing). Associations were considered statistically significant if the 95% CI did not overlap 1.

Results

The cohort totaled 1 585 883 individuals (mean [SD] age, 66.8 [14.5] years; 862 585 female [54.4%]), of whom 1 012 400 individuals (mean [SD] age, 73.5 [10.3] years) received updated mRNA COVID-19 vaccines containing the JN.1 lineage vaccine during follow-up (**Table**). No statistically significant increases in the rate of hospital contacts for any of 29 adverse events were observed during the 28-day risk period after receipt of a JN.1-containing mRNA vaccine compared with reference period rates (**Figure**). For example, the incidence rate ratio was 0.84 (95% CI, 0.76-0.94) for ischemic cardiac events, 0.92 (95% CI, 0.76-1.13) for intracranial bleeding, and 1.12 (95% CI, 0.41-3.10) for myocarditis.

Discussion

In this nationwide cohort study, no increased risk of 29 adverse events was observed after vaccination with the updated COVID-19 mRNA vaccine containing the SARS-CoV-2 Omicron JN.1 lineage in approximately 1 million adults. Limitations include that residual confounding and health care use bias cannot be excluded even with the use of within-individual comparisons. Additionally, although we analyzed a nationwide cohort, some outcomes, such as erythema multiforme, occurred very rarely during follow-up, with consequently lower statistical precision, and some outcomes, such as transverse myelitis, could not be statistically compared. Notably, the upper bound of the CI for 19 of 29 adverse events examined was inconsistent with moderate to large increases in relative risks of more than 1.5.

ARTICLE INFORMATION

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Author Contributions: Dr Andersson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Andersson.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Andersson, Thiesson.

Supervision: Hviid.

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Data Sharing Statement: See Supplement 2.

REFERENCES

1. Food and Drug Administration. FDA approves and authorizes updated mRNA COVID-19 vaccines to better protect against currently circulating variants. FDA. August 22, 2024. Accessed December 5, 2024. https://www.fda.gov/news-events/press-announcements/fda-approves-and-authorizes-updated-mrna-covid-19-vaccines-better-protect-against-currently

2. European Medicines Agency. ETF recommends updating COVID-19 vaccines to target new JN.1 variant. EMA. April 30, 2024. Accessed December 5, 2024. https://www.ema.europa.eu/en/news/etf-recommends-updating-covid-19-vaccines-target-new-jn1-variant

3. Brighton Collaboration. COVID-19 AESI list 5th update—October 2022. November 11, 2022. Accessed October 1, 2024. https://brightoncollaboration.org/covid-19-aesi-list-5th-update-october-2022/

4. Tworkoski E, Zhou CK, Wong HL. *Biologics effectiveness and safety (BEST) initiative: background rates of adverse events of special interest for COVID-19 vaccine safety monitoring*. Center for Biologics Evaluation and Research Office of Biostatistics and Epidemiology; 2021. Accessed October 4, 2024. https://bestinitiative.org/wp-content/uploads/2022/01/C19-Vaccine-Safety-AESI-Background-Rate-Report-2021.pdf

5. Andersson NW, Thiesson EM, Hansen JV, Hviid A. Safety of BA.4-5 or BA.1 bivalent mRNA booster vaccines: nationwide cohort study. *BMJ*. 2023;382:e075015. doi:10.1136/bmj-2023-075015

6. Andersson NW, Thiesson EM, Hviid A. Adverse events after XBB.1.5-containing COVID-19 mRNA vaccines. *JAMA*. 2024;331(12):1057-1059. doi:10.1001/jama.2024.1036

SUPPLEMENT 1.

eTable. Eligibility criteria, outcome, and covariate definitions
eFigure. Schematic figure of the study design
eReferences.

SUPPLEMENT 2.

Data Sharing Statement

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